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Multicenter evaluation of the hemolysis index in automated clinical chemistry systems

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Abstract

Background: In vitro hemolysis, the prevailing cause of preanalytical error in routine laboratory diagnostics, might influence the reliability of several tests, affect the quality of the total testing process and jeopardize patient safety. Although laboratory instrumentation is now routinely equipped with systems capable of automatically testing and eventually correcting for hemolysis interference, to our knowledge there are no reports that have compared the efficiency of different analytical platforms for identifying and classifying specimens with hemolysis.
Methods: Serum from a healthy volunteer was spiked with varying amounts of hemolyzed blood from the same volunteer, providing a serum free hemoglobin concentration ranging from 0.0 g/L to 2.0 g/L as measured by the reference cyanmethemoglobin assay. The spiked serum samples were shipped to seven separate laboratories and the hemolysis index (HI) was tested in triplicate on the following analytical platforms: Roche Modular System P (n = 4) and Integra 400 Plus (n = 1), Siemens Dimension RxL (n = 3), ADVIA 2400 (n = 1) and ADVIA 1800 (n = 1), Olympus AU 680 (n = 1) and Coulter DXC 800 (n = 1).
Results: Satisfactory agreement of HI results was observed among the various analytical platforms, despite a trend toward overestimation by the ADVIA 2400 and 1800. After normalizing results according to the instrument-specific alert value, discrepancies were considerably reduced. All instruments except for the Dimension RxL gave values normalized to the instrument-specific alert value, <1.0 for the sample with 0.048 g/L free hemoglobin, and >1.0 for the sample with 0.075 g/L free hemoglobin. The results of the four Modular System P tests were also highly reproducible among the different facilities. When evaluating instruments that provided quantitative HI results, the mean intra-assay coefficient of variation (CV) calculated for the triplicate determinations was always between 0.1% and 2.7%.
Conclusions: The results of this multicenter evaluation confirm that efficiency of different analytical platforms to correctly identify and classify unsuitable samples is satisfactory. However, more effort should be placed on the standardization of reporting HI. All the instruments that we tested provide either quantitative or qualitative results that are essentially comparable, but which should always be compared with the instrument-specific alert values to harmonize their efficiency.
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Keywords: errors; hemolysis; hemolysis index (HI); patient safety; preanalytical variability.

Introduction

Preanalytical variability is a major problem in laboratory diagnostics because several phases of this process can affect specimen integrity and the reliability of test results. Spurious test results obtained on unsuitable specimens not only impact the quality of the total testing process, but might produce adverse clinical and economic outcomes. Several lines of evidence show that in vitro hemolysis is the most prevalent preanalytical error; its frequency reportedly affecting as many as 3.3% of routine samples referred to the clinical laboratory, and accounting for up to 70% of all the unsuitable specimens received (1–7). Hemolysis is commonly defined as the release of hemoglobin from erythrocytes into the surrounding plasma as a result of damage or breakdown of the

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cell membrane. Hemolysis confers a pink to red hue coloration of the plasma or serum following centrifugation of specimens. Traditionally, the upper reference limit for free hemoglobin varies from 0.02 mg/L (plasma) to 0.05 mg/L (serum), and it becomes visually detectable when such concentration exceeds 0.3–0.6 g/L (18.8–37.6 μmol/L), corresponding roughly to 0.5%–1.0% of lysed erythrocytes (7).

The interference effect from hemolysis in laboratory diagnostics is a consequence of several coexisting biological and analytical causes, including (a) leakage of hemoglobin and other intracellular components into the surrounding fluid thereby producing false elevations of intracellular analytes or dilutional effects, (b) method- and analyte-dependent spectrophotometric interferences and (c) chemical interference in a variety of analytic reactions. At high concentrations of serum hemoglobin, all these interference effects might coexist, thereby producing spurious variations that do not necessarily follow the same pattern resulting in overestimation or underestimation (1, 2, 7, 8). The magnitude of this problem is further magnified by the management of hemolytic specimens in the laboratory, from their identification to the optimal means of handling them. One of the more debated issues is the identification of hemolysis by laboratory personnel, because hemolysis in serum or plasma is undetectable until the specimen has been centrifuged. However, even following centrifugation there are no definitive guidelines, other than recommendations or suggestions, that define what means should be used to assess the degree of hemolysis or what thresholds should be used to guide the rejection of samples (7).

In vitro hemolysis has traditionally been assessed on an arbitrary basis through visual inspection by laboratory personnel. More recently, however, several preanalytical modules and analytical platforms have been equipped with systems capable of automatically testing and eventually correcting for a broad series of analytical interferences, including hemolysis. In most cases, the instruments report a qualitative or quantitative ''hemolysis index'' (HI), which should be compared with manufacturer-, instrument- and analyte-specific alert values before deciding whether to perform testing. This process is not intended for diagnostic purposes, but instead used to determine the condition of a sample. The user often can adjust the level at which the interference generates a flag, and also can customize the operating mode to reflect their own individual operating requirements for reporting interference. The implementation of this technology offers several advantages. It can overcome the inherent limits of visual inspection and it helps to improve the recognition of specimens with mild hemolysis (~0.6 g/L of free hemoglobin) which are difficult to detect by visual inspection but might still be unsuitable for the measurements of several analytes such as aspartate aminotransferase, lactate dehydrogenase and potassium (8). The index may also be useful as a quality assurance indicator to evaluate and improve the best preanalytical practices among different blood collection sites or hospital wards. Finally, the automated HI allows standardization and harmonization of behavior among operators in the same laboratory or among different facilities. Although widespread implementation of this technology is thus advantageous, advisable and even recommended (7, 9), there are no reports, to the best of our knowledge, that have compared the efficiency of different analytical platforms for the identification and correct classification of hemolyzed specimens.

Materials and methods

The preparation of the samples was performed at a central location in the Clinical Chemistry Laboratory of the Verona University Hospital. On the morning of day 1, 50 mL of blood were collected from a healthy volunteer into 10 siliconized vacuum tubes containing no additives (BD Vacutainer® Serum Glass Tubes, 5.0 mL; Cat# 367614, Becton Dickinson UK Ltd, Plymouth, UK), using a BD Vacutainer® Multi-sample 21G needle (Becton Dickinson). One 5 mL specimen (hemolyzed sample – 5 mL of whole blood) was immediately stored at –70°C, whereas the other nine samples were centrifuged at 1500×*g* for 10 min at room temperature. The serum was separated and pooled from the nine tubes, creating ~22 mL (pooled sample), and also stored at –70°C. On the morning of day 2, the hemolysed sample and the pooled sample were thawed and re-centrifuged at 1500×*g* for 10 min. Free hemoglobin was quantitated in the supernatant of the hemolyzed sample by the reference cyanmethemoglobin method using a UV-1700 spectrophotometer (Shimadzu Italia S.I.r., Milan, Italy) (10). Five serial dilutions of free serum hemoglobin were further prepared by mixing serial aliquots of hemolyzed sample and pooled sample to achieve final free hemoglobin concentrations ranging from 0.09 g/L to 2.0 g/L (labeled as Sample A, B, C, D and E). These concentrations approximately cover the degree of hemolysis seen in most hemolyzed samples encountered by clinical

Table 1 Description of centers and instrumentation.

Laboratory	Instruments[a]
University Hospital, Verona, Italy	Roche Modular System P and Siemens Dimension RxL
University Hospital, Padova, Italy	Roche Modular System P and Siemens Dimension RxL
San Bortolo Hospital, Vicenza, Italy	Siemens ADVIA 2400 and 1800
Hôpital Saint Antoine, Paris, France	Olympus AU 680 and Beckman Coulter DxC 800
University Hospital, Leuven, Belgium	Roche Modular System P and Siemens Dimension RxL
University Hospital, Hradec Kralove, Czech Republic	Roche Modular System P
BD PAS, European Clinical Laboratory, Plymouth, UK	Roche Integra 400 Plus

[a]F. Hoffmann-La Roche Ltd., Basel, Switzerland; Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA; Olympus Medical System Corp., Tokyo, Japan; Beckman Coulter Inc., Fullerton, CA, USA.

Table 2 Description of the instrumentation used to test the hemolysis index (HI) and the instrument-specific alert values.

Manufacturer	Instrument	Alert value (free hemoglobin)
Beckman	Coulter DxC 800	2 (arbitrary unit, corresponding to 0.50–1.0 g/L)
Olympus	AU 680	''+'' (arbitrary unit, corresponding to 0.50–1.0 g/L)
Roche	Modular System P	0.60 g/L
Roche	Integra 400 PLUS	0.60 g/L
Siemens	RxL Dimension	2 (arbitrary unit, corresponding to 0.25–0.50 g/L)
Siemens	ADVIA 2400	0.80 g/L[a]
Siemens	ADVIA 1800	0.80 g/L[a]

[a]Arbitrary cut-off established by the local operator.

laboratories (4). For each of these separate samples, seven aliquots of 0.6 mL each were transferred into 1 mL plastic cups and shipped to the laboratories participating in this study (Table 1). Samples were kept stored until all laboratories had received their samples. The tests were performed simultaneously in the seven laboratories participating in the study. Before assessment, the samples were mixed manually by 5–6 complete inversions. The HI was tested on each sample (from A to E) in triplicate on the analytical platforms reported in Table 3, and quantitative results were reported as mean ± SD. Concomitantly, the hemoglobin concentration of each sample was retested by the cyanmethemoglobin method in the Clinical Chemistry Laboratory of the Verona University Hospital. When quantitative results were available, results were normalized to the instrument-specific alert value (i.e., measured value/alert value) as provided by the manufacturers (Table 2). In addition, an arbitrary threshold of free hemoglobin measured by the cyanmethemoglobin method was established at 0.6 g/L. This concentration of free hemoglobin is suggestive of a mildly hemolyzed specimen and represents the threshold for deciding whether some test results might already be significantly affected by in vitro hemolysis (e.g., aspartate aminotransferase, lactate dehydrogenase and potassium) (8).

Results

The results of this multicenter evaluation of the HI are shown in Tables 3 and 4. No variation in the free hemoglobin concentration in the specimens was observed prior to and following shipment, as verified by the cyanmethemoglobin measurement (Passing and Bablok regression analysis and Pearson correlation coefficient: [before shipment] = 1.02 × [after shipment] + 0.01; $r = 1.00$; $p < 0.001$). Satisfactory agreement was observed among the various analytical platforms, despite the presence of a trend toward overestimation by both the ADVIA 2400 and 1800 Dimension (Table 3). However, after normalizing results according to the instrument-specific alert value (i.e., [measured value]/[0.6 g/L] for the cyanmethemoglobin method, and [measured value]/[highest alert value] for the instruments), such discrepancies were considerably reduced (Table 4). In particular, all instruments except for the RxL Dimension gave ''normalized'' values < 1.0 for sample B (free hemoglobin value of 0.048 g/L by the cyanmethemoglobin method) and > 1.0 for sample C (free hemoglobin value of 0.075 g/L by the cyanmethemoglobin method). The quantitative HI results obtained on the Modular System P were also highly reproducible among the different facilities, as demonstrated by the non-significant variation ($p = 0.911$ by Kruskal-Wallis test) and the excellent correlation shown by Passing and Bablok regression analysis and the Pearson correlation coefficient (Table 5). The triplicate measurements using instruments providing semi-quantitative HI results were always identical for all the samples tested. For those instruments providing quantitative HI results, the mean intra-assay coefficient of variation (CVs) calculated for the triplicate determinations were 1.2% for the Modular System P, 2.7% for the Integra 400 Plus, 0.1% for the ADVIA 2400 and 1.0% for the ADVIA 1800, respectively.

Discussion

The receipt of hemolyzed samples in clinical laboratories is common and their identification is often difficult, especially when using arbitrary procedures such as the visual inspection. Detection of unsuitable specimens is even more challenging, if not impossible, when using whole blood specimens on point of care (POC) devices. Discrepant potassium results between POC devices and conventional laboratory instrumentation, rarely recorded, might be due to unrecognized in vitro hemolysis (11). Although quantitation of free hemoglobin in serum or plasma is theoretically possible by immunonephelometry (12), the use of this approach on all samples referred for testing is unpractical due to resultant increases in turnaround time, unavailability of the assay on instruments and uneconomical. Therefore, to simplify and standardize the process of identification of hemolyzed samples, and to evaluate their suitability for testing, automated detection of spectrophotometric interferents in patient serum and plasma caused by hemolysis, as well as by icterus and lipemia, have been developed. These systems consist of rapid, simple and inexpensive spectrophotometric blanked bichromatic measurements, most frequently between 405 nm and 700 nm (13). These flexible features are designed to provide users with an optional, automated and unbiased means of identification, so that unsuitable specimens can be dealt with according to the best laboratory practice. There is little doubt that the widespread implementation of the HI, as well as other serum indexes, would be advantageous and profitable for a variety of reasons. These include the rapid detection of in vivo or in vitro hemolysis and the assessment of potential interference from hemo-

Table 3 Results (g/L) of the hemolysis index (HI) evaluated on the different analytical platforms. Quantitative results are reported as mean ± SD.

	Cyanmethemoglobin method	Modular System P					Integra 400 Plus	ADVIA 2400	ADVIA 1800	Coulter DxC 800	AU 680	Dimension RxL			
		Verona	Leuven	Hradec Kralove	Padova	Mean						Verona	Leuven	Padova	Mean
Sample A	0.09 ± 0.01	0.09 ± 0.00	0.10 ± 0.01	0.09 ± 0.00	0.09 ± 0.01	0.09 ± 0.01	0.12 ± 0.01	0.12 ± 0.00	0.14 ± 0.01	0.00	< 0.50	< 0.25	< 0.25	< 0.25	< 0.25
Sample B	0.48 ± 0.02	0.44 ± 0.01	0.50 ± 0.01	0.45 ± 0.02	0.45 ± 0.02	0.46 ± 0.03	0.48 ± 0.02	0.65 ± 0.00	0.72 ± 0.01	0–0.50	< 0.50	0.25–0.50	0.25–0.50	0.25–0.50	0.25–0.50
Sample C	0.75 ± 0.02	0.70 ± 0.00	0.79 ± 0.01	0.71 ± 0.01	0.70 ± 0.01	0.73 ± 0.04	0.74 ± 0.01	1.03 ± 0.00	1.14 ± 0.00	0.50–1.00	0.50–1.00	0.50–2.00	0.50–2.00	0.50–2.00	0.50–2.00
Sample D	1.19 ± 0.03	1.13 ± 0.01	1.26 ± 0.01	1.16 ± 0.00	1.13 ± 0.01	1.18 ± 0.06	1.18 ± 0.02	1.66 ± 0.01	1.82 ± 0.02	1.00–1.50	1.00–2.00	0.50–2.00	0.50–2.00	0.50–2.00	0.50–2.00
Sample E	2.17 ± 0.03	2.08 ± 0.02	2.30 ± 0.02	2.12 ± 0.01	2.07 ± 0.01	2.16 ± 0.11	2.13 ± 0.01	3.03 ± 0.02	3.34 ± 0.01	2.50–3.00	2.00–3.00	2.00–3.00	2.00–3.00	2.00–3.00	2.00–3.00

Table 4 Results normalized to the instrument-specific alert value ([measured value]/[0.6 g/L] for the cyanmethemoglobin method, and [measured value]/[highest alert value] for the instruments) of the hemolysis index (HI) evaluated on the different analytical platforms.

	Cyanmethemoglobin method	Modular System P					Integra 400 Plus	ADVIA 2400	ADVIA 1800	Coulter DxC 800	AU 680	Dimension RxL			
		Verona	Leuven	Hradec Kralove	Padova	Mean						Verona	Leuven	Padova	Mean
Sample A	0.14	0.15	0.17	0.15	0.14	0.16	0.20	0.15	0.17	< 0.50	< 0.50	< 0.50	< 0.50	< 0.50	< 0.50
Sample B	0.80	0.73	0.83	0.75	0.74	0.77	0.79	0.81	0.90	0.00–0.50	< 0.50	**0.50–1.00**	**0.50–1.00**	**0.50–1.00**	**0.50–1.00**
Sample C	**1.25**	**1.17**	**1.31**	**1.19**	**1.17**	**1.22**	**1.24**	**1.29**	**1.43**	**0.50–1.00**	**0.50–1.00**	**1.00–4.00**	**1.00–4.00**	**1.00–4.00**	**1.00–4.00**
Sample D	**1.98**	**1.88**	**2.11**	**1.93**	**1.89**	**1.97**	**1.96**	**2.07**	**2.28**	**1.00–1.50**	**1.00–2.00**	**1.00–4.00**	**1.00–4.00**	**1.00–4.00**	**1.00–4.00**
Sample E	**3.62**	**3.46**	**3.83**	**3.53**	**3.46**	**3.60**	**3.55**	**3.79**	**4.18**	**2.50–3.00**	**2.00–3.00**	**4.00–6.00**	**4.00–6.00**	**4.00–6.00**	**4.00–6.00**

Data in bold refer to samples which would have been considered unsuitable for the measurement of some analytes (e.g., aspartate aminotransferase, lactate dehydrogenase and potassium) on each specific analytical platform.

Table 5 Passing and Bablok regression analysis and Pearson correlation coefficient for the HI assayed on the four Roche Modular System P platforms.

	Padova	Leuven	Hradec Kralove
Verona	$y=0.994x$ $r=1.00$; $p<0.001$	$y=1.104x+0.01$ $r=1.00$; $p<0.001$	$y=1.021x$ $r=1.00$; $p<0.001$
Padova	–	$y=1.111x$ $r=1.00$; $p<0.001$	$y=1.029x–0.01$ $r=1.00$; $p<0.001$
Leuven	–	–	$y=0.923x$ $r=1.00$; $p<0.001$

globin-based oxygen carriers (14), which would ultimately help diminish uncertainty in the preanalytical phase, enhance the quality in laboratory diagnostics, and reduce the chance of errors that can jeopardize the patient safety (7). Although the approach has been previously questioned (7), it is necessary to mention that the availability of quantitative results of hemoglobin in the samples might allow the use of formulas for correcting biases due to interference from hemolysis (15).

Although most preanalytical workstations and clinical chemistry platforms are now equipped with automatic systems for detecting, and some for quantitating interferents, no studies have previously assessed imprecision and reproducibility of these measures among facilities and, especially, among different instruments and manufacturers. The results of this multicenter evaluation demonstrate that overall imprecision of the instruments tested is satisfactory, as shown by inter-assay CVs between 0.1% and 2.7%. We have also shown that the reproducibility among different facilities using the same instrument (Modular System P) is excellent. The overall instrument-specific efficiency for identifying unsuitable samples was highly comparable, and no false negative results occurred when analyzing samples with free hemoglobin concentrations >0.6 g/L. Likewise, all instruments except for the RxL Dimension correctly classified sample B, with a hemoglobin concentration of 0.048 g/L as measured by the cyanmethemoglobin method, suitable for testing. These results are of particular significance in situations such as total laboratory automation or in laboratories where the preanalytical workstations are connected directly to the analytical platform and workflow makes visual inspection virtually impossible. However, we have also demonstrated that more efforts should be placed on standardization of reporting of HI. In addition to previous concerns that have been raised regarding the sometimes arbitrary and lack of evidence-based cutoffs to define the limits at which clinically significant interference starts (16), all the instruments that we tested provide either quantitative or qualitative results that are roughly comparable, but which should always be linked to the instrument-specific alert value for each test in order to harmonize and streamline their effectiveness (Tables 3 and 4). It is also important to highlight that it is necessary to evaluate the influence of hemolysis for each test and to state the limits of acceptability for each, as proposed in some validation protocols (17, 18). Unfortunately, we could not evaluate the HI on other instruments than those available to the participants of the study group. Thus, these results might not be universally applicable to other testing systems.

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